REMARKS

Applicant appreciates the thorough examination of the present application as evidenced by the final Office Action dated January 9, 2008 (hereinafter, "Office Action").

The specification is amended herein to incorporate a Substitute Sequence Listing that includes SEQ ID NO:5, corresponding to the mature form of EMAP II, and SEQ ID NO:6, corresponding to SEQ ID NO:1, but without the initial cysteine residue. The specification has also been amended to insert these SEQ ID NOs into the specification. Support for SEQ ID NO:5 and the text added to the paragraph on page 5, lines 15-23, may be found in Figure 4A-4D and column 29, lines 28-31, in Stern et al., U.S. Patent No. 5,641,867, which is incorporated by reference in the present application. Support for SEQ ID NO:6 may be found on page 13, lines 7-13 of the specification as filed. No new matter is added by the amendments to the specification, and their entry is respectfully requested.

Applicant hereby states in support of filing a sequence listing under 37 C.F.R. § 1.821(f) that the content of the paper and computer readable copies of the Sequence Listing, submitted concurrently herewith in accordance with 37 CFR § 1.821(c) and (e), are the same; and as required under 37 CFR § 1.821(h) that the paper and computer readable copies of the Sequence Listing submitted concurrently herewith contain no new matter, nor do they go beyond the disclosure of the application as filed.

Claims 1-4, 6-14, 16-19 and 47-57 are pending in the present application. Withdrawn claims 55-57 are canceled herein without prejudice. Claims 58-67 are added herein to complete the record, and read on the invention elected for examination with Applicant's response of September 4, 2001 (Group I, methods for facilitating vascular growth in a subject via administration of an inhibitor/antagonist of EMAP II; species election: antibodies to EMAP II).

I. Interview Summary

Applicant would like to thank Examiner Janet L. Epps Ford for the phone interview conducted on April 22, 2008, with Applicant's representatives, Shawna Cannon Lemon and Sherry L. Murphy. Applicant concurs with the Interview Summary mailed on April 28, 2008.

Proposed additions to the claims were discussed, with claims directed to antibodies specifically binding to an EMAP II amino acid sequence corresponding to the cleaved form, and to the 13-mer polypeptide used to raise antibodies in the specification Examples. The Examiner indicated that a new search may be needed for their examination.

The outstanding rejection under the enablement requirement was discussed. The Examiner requested that a Declaration of Applicant Dr. Margaret Schwarz (hereinafter "Declaration") be submitted to indicate on the record that the antibodies used in Example 1 of the specification were also used in the Thompson et al. publication, and also to confirm that the Examiner's understanding of Example 1 was correct, namely, that Example 1 used polyclonal antibodies raised against the 13-mer reported in Example 2. The requested Declaration is attached to the present response.

The Murray et al. reference was also discussed with respect to enablement, but no agreement was reached.

In light of the helpful and constructive dialog provided by the Examiner, Applicant herein provides further remarks in support of the enablement of the pending claims.

II. Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-4, 6-14, 16-19 and 47-54 stand rejected under 35 U.S.C. § 112, first paragraph, enablement. This rejection is respectfully traversed.

A. Legal Standard of Enablement

The test for enablement is whether one skilled in the art could reproduce the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The key word is "undue," not "experimentation," and "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804, 807 (CCPA 1982)). In *Wands*, claims to antibodies that required a screening procedure to isolate the desired hybridoma cells from enormous numbers of other cells present in the reaction mixture were held to not require experimentation that was "undue." *Id.*, 8 USPQ2d at 1406. The amount of effort required to make the antibodies was "not excessive." *Id.*, 8 USPQ2d at 1407.

B. Points Raised in the Office Action

The Office Action states on Pages 3-4:

1) the biologically active form of EMAP II was uncertain as of the filing date of the instant application;

2) further experimentation was required to understand its role *in vivo*; and

3) experimental data based upon the use of antibodies targeting a peptide fragment that is not found in SEQ ID NO: 4 (namely, SEQ ID NO:1) is not sufficient to provide sufficient guidance to practice the full scope of the claimed invention.

Reconsideration of each of these points is respectfully requested in view of the discussion presented below.

1) The Biologically Active Form of EMAP II

Applicant respectfully submits that it was known in the art at the time of filing that EMAP II is transcribed as a precursor form and is processed into a mature form. See Kao et al., "Characterization of a Novel Tumor-derived Cytokine," Journal of Biological Chemistry, 269(40):25106-25119 (1994) (submitted with Information Disclosure Statement of May 11, 2001). "[T]he precursor of EMAP II is a unique, leaderless, single polypeptide chain with predicted molecular mass ~ 34kDa," and the "mature form released by Meth A cells corresponds to ~ 20kDa." (Abstract, page 25106). Figure 1 on page 25109 of Kao et al. shows the deduced amino acid sequences for murine and human pro-EMAP II, and shows where pro-EMAP II is cleaved to form the mature form of EMAP II.

In addition, Figures 4A-4D of Stern et al., U.S. Patent No. 5,641,867, incorporated by reference in the present application, shows a sequence alignment of the human and murine EMAP II. In Figure 4B, the arrow indicates where EMAP II is cleaved to form the mature protein. See also column 29, lines 18-39, which describes how this cleavage site was experimentally determined.

Accordingly, the evidence of record in the present application demonstrates that the biologically active form of EMAP II was known in the art at the time of filing.

2) EMAP II Distribution *in vivo*

The Office Action states on Page 5 that the Murray et al. reference notes that a comprehensive distribution of the EMAP II protein *in vivo* was not known prior to their studies, pointing to page 2046, 4th paragraph.

It is Applicant's view that the Murray et al. reference supports enablement of Applicant's invention by confirming that EMAP II is present in cardiac muscle tissue. "[W]hether or not an invention would be deemed operative by one of ordinary skill in the art is determined, not at the time the invention was made but rather (at the earliest) at the time of

the examiner's call for proof." In re Pottier, 376 F.2d 328, 330 n.1, 153 USPQ 407, 408 n.1 (CCPA 1967).

Further support of the presence of EMAP II in cardiac tissue is found in Thompson et al., which states, "high levels of EMAP II are expressed throughout the 6-week period following myocardial infarction." (page 162, bottom of first column). This statement supports the distribution of EMAP II in cardiac muscle.

Therefore, Applicant respectfully asserts that there is no reason to doubt that EMAP II is present in cardiac muscle *in vivo* consistent with the teachings and claims of the present application.

3) Experimental Data Reported in the Specification

Following the helpful suggestions of the Examiner, Applicant herein provides a Declaration stating that the antibodies used in Example 1 of the specification were also used in the Thompson et al. publication. The Declaration further states that the Examiner's understanding of Example 1 was correct in that Example 1 used polyclonal antibodies raised against the 13-mer reported in Example 2 (see Office Action at Page 4).

This 13-mer is found at amino acids 254-266 of the EMAP II sequence of SEQ ID NO:4, which is towards the C-terminal region of the protein. The following is a sequence alignment which shows where in the pro-EMAP II protein (SEQ ID NO:4) the mature EMAP II (SEQ ID NO:5) and the 13-mer polypeptide (SEQ ID NO:6) are located.

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SEQ ID NO:5   ------------------------------------------------------------

SEQ ID NO:4  1 MANNDAVLKRLEQKGAEADQIIEYLKQQVSLLKEKAILQATLREEKKLRVENAKLKKEIE 60
                        .         20         .         40         .         60

              ------------------------------------------------------------

             61 ELKQELIQAEIQNGVKQIAFPSGTPLHANSMVSENVIQSTAVTTVSSGTKEQIKGGTGDE 120
                        .         80         .        100         .        120
                                                  .        20         .
              1 ---------------------------SKPIDVSRLDLRIGCIITARKHPDADSLYVEEVD 34
                                            SKPIDVSRLDLRIGCIITARKHPDADSLYVEEVD
            121 KKAKEKIEKKGEKKEKKQQSIAGSADSKPIDVSRLDLRIGCIITARKHPDADSLYVEEVD 180
                        .        140         .        160         .        180
                 40         .         60         .         80         .
             35 VGEIAPRTVVSGLVNHVPLEQMQNRMVILLCNLKPAKMRGVLSQAMVMCASSPEKIEILA 94
                VGEIAPRTVVSGLVNHVPLEQMQNRMVILLCNLKPAKMRGVLSQAMVMCASSPEKIEILA
            181 VGEIAPRTVVSGLVNHVPLEQMQNRMVILLCNLKPAKMRGVLSQAMVMCASSPEKIEILA 240
                        .        200         .        220         .        240
                100         .        120         .        140         .
             95 PPNGSVPGDRITFDAFPGEPDKELNPKKKIWEQIQPDLHTNDECVATYKGVPFEVKGKGV 154
                PPNGSVPGDRITFDAFPGEPDKELNPKKKIWEQIQPDLHTNDECVATYKGVPFEVKGKGV
            241 PPNGSVPGDRITFDAFPGEPDKELNPKKKIWEQIQPDLHTNDECVATYKGVPFEVKGKGV 300
                        .        260         .        280         .        300
                 160        SEQ ID NO:6
            155 CRAQTMSNSGIK                                                166
                CRAQTMSNSGIK
            301 CRAQTMSNSGIK                                                312
                        .

 % Identity =  53.2 (166/312)       % Homology =   0.0 (0/312)       % Total =  53.2 (166/312)
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In addition, Stern et al. (U.S. Patent No. 5,641,867, incorporated by reference in the present application) reports that an antibody raised against a sequence in the N-terminal region of mature EMAP II (SEQ ID NO: 5 in the present application) also functions to block the activity of EMAP II. See, e.g., column 10, lines 1-33; column 13, lines 56-63:

> Antibodies to the ~22 kDa polypeptide were prepared by immunizing rabbits with a synthetic peptide comprising the amino terminal sequence coupled to keyhold limpet hemocyanin. IgG from this antiserum neutralized the ability of the ~22 kDa meth A factor to induce tissue factor activity in ECs in a dose-dependent manner and adsorbed the activity when the antibody was bound to a solid support. In contrast, non-immune IgG was without effect.

In view of the working examples provided in the present specification, which demonstrate that antibodies prepared against different regions of the EMAP II protein block the function of EMAP II, Applicant respectfully asserts that one of skill in the art would conclude that the pending claims directed to an antibody that specifically binds to EMAP II of SEQ ID: 4 are enabled by the application as filed.

C. The Breadth of the Pending Claims

Regarding the breadth of the pending claims, Applicant notes that the claims are specific in reciting human treatment with regard to cardiac muscle tissue with antibodies that specifically bind to a particular human EMAP II amino acid sequence (SEQ ID: 4). Therefore, this factor weighs in Applicant's favor.

D. Conclusion – Claims Are Enabled

Having adequately addressed the points raised in the Office Action with respect to enablement, Applicant respectfully submits that there is no reason to doubt that enablement is satisfied for the claimed invention (see M.P.E.P. § 2164.04). Accordingly, Applicant respectfully requests that the rejection of Claims 1-4, 6-14, 16-19 and 47-54 under 35 U.S.C. § 112, first paragraph, enablement, be withdrawn.

III. New Claims 58-67

New claims 58-67 are added herein to complete the record. Claims 58-64 are directed to an antibody that specifically binds to EMAP II of SEQ ID NO:5 (mature EMAP II), and claims 65-67 are directed to an antibody that specifically binds to EMAP II of SEQ ID NO:6 (the 13-mer peptide sequence). These sequences are found in SEQ ID NO:4, as shown in the

sequence alignment listed above.

Applicant respectfully submits that these new claims are adequately enabled for at least the reasons stated above with respect to Claims 1-4, 6-14, and 16-19 and 47-54. In addition, claims 58-67 are directed to an antibody that specifically binds to a more particular region of the EMAP II protein, which recitation further supports the enablement of these claims.

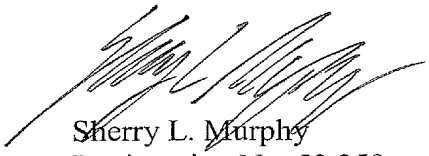
IV. Conclusion

In view of the foregoing amendments and remarks addressing the points raised in the Office Action of January 9, 2008, Applicant respectfully requests that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course.

The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

A petition and fee for a one-month extension of time are filed herewith. No additional fees are believed due. In the event that additional extension is necessary to allow consideration of this paper, such an extension is hereby petitioned for under 37 C.F.R. § 1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,



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Attachments: Substitute Sequence Listing (7 pages);
Declaration Under 37 C.F.R. § 1.132 of Margaret A. Schwarz, M.D. (2 pages);
and Exhibit A of the Declaration (17 pages)